PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: Bill T. Brazil

By

WYETH
Patent Law Department
Attn. Brazil, Bill T.
Five Giralda Farms
Madison, New Jersey 07940
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 09/09/2005
Applicant's or agent's file reference AM101358	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2004/041803	International filing date *(day/month/year)* 10/12/2004
Applicant WYETH	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Barbara Klaver

Express Mail No. EQ543967205US

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PA .NT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
AM101358		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/041803	10/12/2004	17/12/2003
Applicant		
WYETH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [X] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/041803

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-23,57,60,63-85,119 and 122 (all totally)

Process for producing storage stable virus composition comprising a) freezing the virus composition below its glass transition temperature in a time of 60 minutes or less, and b) lyophilizing the virus composition.

1.1. claims: 22,84 (totally) and 1-21,57,60,63-83,119,122 (all partially)

Process for producing storage stable virus composition comprising a) freezing the virus composition below its glass transition temperature in a time of 60 minutes or less, and b) lyophilizing the virus composition, and wherein the temperature in step a) is decreased from 5 degree C to minus 50 degree C at a rate of about minus 1 degree C per minute to about minus 2 degree C per minute, and maintained at minus 50 degree C for 60 minutes.

1.2. claims: 23,85 (totally) and 1-21,57,60,63-83,119,122 (all partially)

Process for producing storage stable virus composition comprising a) freezing the virus composition below its glass transition temperature in a time of 60 minutes or less, and b) lyophilizing the virus composition, and wherein in step a) the vial containing the virus composition is placed on a lyophilization shelf at minus 70 degree C and held at minus 70 degree C for about 60 minutes.

---

2. claims: 24-42,58,61,86-104,120,123 (all totally)

Process for producing a lyophilization stable bulk volume virus composition comprising a) placing a liquid virus composition having a volume of at least 50 ml in a lyophilization tray, b) freezing the virus composition below its glass transition temperature for at least about 20 minutes in a liquid nitrogen bath and c) lyophilizing the virus composition.

---

3. claims: 43-56,59,62,105-118,121,124 (all totally)

Process for producing storage stable liquid virus composition comprising steps (a) to (f) of claims 43 or 105.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US2004/041803

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/12 A61K39/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/086443 A (MEDIMMUNE VACCINES, INC; TRUONG-LE, VU; PHAM, BINH, V; CARPENTER, JOHN) 23 October 2003 (2003-10-23) claims 1-3,8,9,11,12,20-24,46,47,49,59 -----	1-19,57, 60, 63-81, 119,122
X	US 4 273 762 A (MCALEER ET AL) 16 June 1981 (1981-06-16) column 3, paragraph 3 - column 4, paragraph 1 ----- -/--	63-83, 119,122

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2005	09. 09. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lonnoy, O

4

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAKOSCHEY B ET AL: "Serum-free produced Bovine Herpesvirus type 1 and Bovine Parainfluenza type 3 virus vaccines are efficacious and safe." CYTOTECHNOLOGY, vol. 39, no. 3, 2002, pages 139-145, XP002333213 ISSN: 0920-9069 table 1	57,60, 119,122
X	TANNOCK G A ET AL: "FREEZE-DRYING OF RESPIRATORY SYNCYTIAL VIRUSES FOR TRANSPORTATION AND STORAGE" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 25, no. 9, 1987, pages 1769-1771, XP008048997 ISSN: 0095-1137 table 2	57,60, 119,122
A	PHILLIPS G O ET AL: "A STUDY OF WATER BINDING IN LYOPHILIZED VIRAL VACCINE SYSTEMS" CRYOBIOLOGY, vol. 18, no. 4, 1981, pages 414-419, XP008049014 ISSN: 0011-2240	
A	WO 02/09749 A (AVENTIS PASTEUR LIMITED; PARRINGTON, MARK; SLOAN, ROBERT, J; SALES, VA) 7 February 2002 (2002-02-07) table 5	
P,X	WO 2004/017990 A (PFIZER PRODUCTS INC; DOMINOWSKI, PAUL, JOSEPH) 4 March 2004 (2004-03-04) page 9, lines 34-36; claim 1	57,60, 119,122
Y	LABCONCO: "FreeZone 1 Liter Benchtop Freeze Dry Systems: User's Manual"[Online] 2003, XP002342295 Retrieved from the Internet: URL:http://www.labconco.com/manual/freeze/FZ1LManual.pdf> [retrieved on 2005-08-25] page 24	24-42, 58,61, 86-104, 120,123
Y	WO 99/62500 A (MERCK & CO., INC; VOLKIN, DAVID, B; BURKE, CARL, J; SHEU, SU-PI) 9 December 1999 (1999-12-09) example 3	24-42, 58,61, 86-104, 120,123

-/--

4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACKSON L A ET AL: "Safety of a trivalent live attenuated intranasal influenza vaccine, FluMist@?, administered in addition to parenteral trivalent inactivated influenza vaccine to seniors with chronic medical conditions" VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 17, no. 15-16, 9 April 1999 (1999-04-09), pages 1905-1909, XP004165037 ISSN: 0264-410X page 1906, column 2, paragraph 1	121,124
A	WO 02/28422 A (SMITHKLINE BEECHAM BIOLOGICALS S.A; COLAU, BRIGITTE, DESIREE, ALBERTE;) 11 April 2002 (2002-04-11) claims 13-15	43-56, 59,62

INTERN[illegible]IONAL SEARCH REPORT

Information on patent family members

Inter[illegible]nal Application No
PCT/US2004/041803

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03086443 A	23-10-2003	AU 2003230908 A1	27-10-2003
		WO 03086443 A1	23-10-2003
		US 2004042972 A1	04-03-2004
US 4273762 A	16-06-1981	AT 6201 T	15-03-1984
		CA 1146861 A1	24-05-1983
		DE 3066651 D1	22-03-1984
		DK 512780 A	04-06-1981
		EP 0030199 A2	10-06-1981
		ES 8205306 A1	16-09-1982
		GR 71638 A1	29-11-1980
		JP 56092822 A	27-07-1981
		PT 72105 A ,B	01-12-1980
WO 0209749 A	07-02-2002	AU 7833701 A	13-02-2002
		WO 0209749 A2	07-02-2002
		CA 2417274 A1	07-02-2002
		EP 1305043 A2	02-05-2003
		US 2004022800 A1	05-02-2004
WO 2004017990 A	04-03-2004	AU 2003263390 A1	11-03-2004
		BR 0313806 A	05-07-2005
		CA 2496750 A1	04-03-2004
		EP 1536830 A1	08-06-2005
		WO 2004017990 A1	04-03-2004
		US 2004081666 A1	29-04-2004
WO 9962500 A	09-12-1999	US 6290967 B1	18-09-2001
		AU 748296 B2	30-05-2002
		AU 4322599 A	20-12-1999
		CA 2333505 A1	09-12-1999
		EP 1083883 A1	21-03-2001
		JP 2002516850 T	11-06-2002
		WO 9962500 A1	09-12-1999
WO 0228422 A	11-04-2002	AU 1398402 A	15-04-2002
		BR 0114393 A	26-08-2003
		CA 2427842 A1	11-04-2002
		CN 1477971 A	25-02-2004
		CZ 20030931 A3	15-10-2003
		WO 0228422 A2	11-04-2002
		EP 1324769 A2	09-07-2003
		HU 0302643 A2	28-11-2003
		JP 2004510744 T	08-04-2004
		NO 20031483 A	28-05-2003
		PL 362705 A1	02-11-2004
		US 2004022808 A1	05-02-2004
		ZA 200302522 A	30-06-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/041803	10.12.2004	17.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/12, A61K39/155

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Lonnoy, O Telephone No. +31 70 340-4294

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/041803

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/041803

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	20-56,59,62,84-118
	No:	Claims	1-19,57,58,60,61,63-83,119-124
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-124
Industrial applicability (IA)	Yes:	Claims	1-124
	No:	Claims	

2. Citations and explanations

see separate sheet

IV. Lack of unity (Continuation)

The application lacks unity of invention as required by Article 3(4)(iii) and Rule 13 PCT for the following reasons:

The prior art provides processes for producing a storage stable virus composition comprising freezing the virus below its glass transition temperature, and lyophilising the virus composition. Document WO03086443 for instance describes a process for producing a storage stable virus composition comprising freezing the virus below its glass transition temperature in a time of less than 60 minutes, and lyophilising the virus composition.

In the light of the prior art, the problem addressed in the present application is the provision of further processes for producing storage stable virus compositions.

A first solution proposed to said problem (claims 22,84 (totally) and 1-21,57,60,63-83,119,122 (all partially)) is a process comprising a) freezing the virus composition below its glass transition temperature in a time of 60 minutes or less, and b) lyophilizing the virus composition, wherein the temperature in step a) is decreased from 5 degree C to minus 50 degree C at a rate of about minus 1 degree C per minute to about minus 2 degree C per minute, and maintained at minus 50 degree C for 60 minutes.

A second solution proposed to said problem (claims 23,85 (totally) and 1-21,57,60,63-83,119,122 (all partially)) is a process comprising a) freezing the virus composition below its glass transition temperature in a time of 60 minutes or less, and b) lyophilizing the virus composition, wherein in step a) the vial containing the virus composition is placed on a lyophilization shelf at minus 70 degree C and held at minus 70 degree C for about 60 minutes.

A third solution proposed to said problem (claims 24-42,58,61,86-104,120,123 (all totally)) is a process comprising a) placing a liquid virus composition having a volume of at least 50 ml in a lyophilization tray, b) freezing the virus composition below its glass transition temperature for at least about 20 minutes in a liquid nitrogen bath and c) lyophilizing the virus composition.

A fourth solution proposed to said problem (claims 43-56,59,62,105-118,121,124 (all totally)) is a process comprising steps (a) to (f) of claims 43 or 105.

Due to the fact that a process for producing a storage stable virus composition comprising freezing the virus below its glass transition temperature in a time of less than 60 minutes, and lyophilising the virus composition is known in the prior art, due to the essential differences between the various solutions, and due to the fact that no other technical feature can be distinguished which, in the light of the prior art could be regarded as special

technical feature, the I.S.A. is of the opinion that the inventions claimed in the present application are not so linked as to form a single inventive concept in the sense of Rule 13.1 PCT. Therefore, the application was found to lack unity of invention. Those inventions which could not be linked by a common inventive concept have been listed as separate subjects. All required addiditonal search fees have been duly paid, and the International Search Report has been established for all inventions. Now, consistently, an opinion with respect to novelty, inventive step and industrial application will be formulated for all inventions.

V. Reasoned statement (Continuation)

Present claims 1,18,19,63,80,81, 24,43,46-48,86,105,108-110 and claims dependent thereon relate to processes defined by reference to desirable properties, namely processes wherein the lyophilized virus composition "is stable for at least one year at a storage temperature of about 1 degree C to about 10 degree C", "has less than about 1.0 log PFU loss after one year of storage at about 1 degree C to about 10 degree C", or "is at least 4.0 log PFU per 0.2 ml after one year of storage at about 1 degree C to about 10 degree C". Said claims lack clarity (Article 6 PCT). An attempt is made to define the processes by reference to a result to be achieved. Consequently, the search had to be carried out as if said desirable properties had not been included in the claims and now, the present opinion has been prepared accordingly.

1. CITATIONS

Reference is made to the following documents:

D1: MAKOSCHEY B ET AL: "Serum-free produced Bovine Herpesvirus type 1 and Bovine Parainfluenza type 3 virus vaccines are efficacious and safe." CYTOTECHNOLOGY, vol. 39, no. 3, 2002, pages 139-145, XP002333213 ISSN: 0920-9069

D2: TANNOCK G A ET AL: "FREEZE-DRYING OF RESPIRATORY SYNCYTIAL VIRUSES FOR TRANSPORTATION AND STORAGE" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 25, no. 9, 1987, pages 1769-1771, XP008048997 ISSN: 0095-1137

D3: WO 03/086443 A (MEDIMMUNE VACCINES, INC; TRUONG-LE, VU; PHAM, BINH, V; CARPENTER, JOHN) 23 October 2003 (2003-10-23)

D4: US-A-4 273 762 (MCALEER ET AL) 16 June 1981 (1981-06-16)

D5: WO2004/017990 (PFIZER PRODUCTS INC) 4 March 2004 (2004-03-04)

D6: LABCONCO: "FreeZone 1 Liter Benchtop Freeze Dry Systems: User's Manual"[Online] 2003, XP002342295 Retrieved from the Internet: URL:http://www.labconco.com/manual/freeze/ FZ1LManual.pdf> [retrieved on 2005-08-25]

D7: WO 99/62500 A (MERCK & CO., INC; VOLKIN, DAVID, B; BURKE, CARL, J; SHEU, SU-PI) 9 December 1999 (1999-12-09)

D8: JACKSON L A ET AL: "Safety of a trivalent live attenuated intranasal influenza vaccine, FluMist@?, administered in addition to parenteral trivalent inactivated influenza vaccine to seniors with chronic medical conditions" VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 17, no. 15-16, 9 April 1999 (1999-04-09), pages 1905-1909, XP004165037 ISSN: 0264-410X

D9: WO 02/28422 A (SMITHKLINE BEECHAM BIOLOGICALS S.A; COLAU, BRIGITTE, DESIREE, ALBERTE;) 11 April 2002 (2002-04-11)

D5 has been cited in the International Search Report as PX document. Should the present application be entered into regional phase before the E.P.O., D5 could be relevant against novelty.

Reasoned statement with regard to novelty, inventive step or industrial applicability of inventions 1 and 2:

2. NOVELTY (Art. 33(2) PCT)

2.1. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-19,57,60,63-83,119 and 122 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

D1 describes the preparation of a.o. bovine parainfluenza type 3 virus in serum-free conditions, and that it is stable after freeze-drying and storage at +4C or -20C for at least one year (Table 1). D1 deprives claims 57, 60, 119 and 122 of novelty, since no technical feature could be identified that would confer novelty over the compositions of D1. In particular, storage stability of the application's compositions and of D1 do not markedly differ.

Similarly, D2 describes freeze-drying of RSV (0.5ml samples), and small-to-negligible loss of infectivity, when held e.g. at 4 degree C for 45 weeks (Table 2). D2 deprives claims 57, 60, 119 and 122 of novelty, since no technical feature could be identified that would

confer novelty over the compositions of D2. In particular, storage stability of the application's compositions and of D2 do not markedly differ.

D3 discloses a process for producing a storage stable virus composition comprising freezing the virus below its glass transition temperature in a time of less than 60 minutes, and lyophilising the virus composition. The process is applicable to a.o. RSV or PIV (claim 3). D3 notably teaches the use in said process of sucrose, human serum albumin, phosphate buffer at pH7.2, and of a first drying step at the glass transition temperature and a second drying step at zero to 50 degrees C. After the initial freezing step (that occurs by immersion in cold liquid, e.g. liquid nitrogen), the rates of temperature ramps are in the tenth of degree Celsius per minute (see e.g. table on page 52). D3 deprives claims 1-19, 57, 60, 63-81, 119 and 122 of novelty.

D4 describes lyophilization of e.g. measle virus aliquots of 0.4ml, by freezing at minus 50C, decreasing pressure, raising temperature to minus 10C over one hour, keeping at minus 10C for one hour, raising temperature to plus 25C over one hour, hold T at 25C for two hours, again reducing pressure, maintaining for an additional two hours, sweeping with Argon and closing the vials. D4 deprives claims 63-83,119,122 of novelty.

3. INVENTIVE STEP (Art. 33(3) PCT)

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter that appears to be novel, i.e. the subject-matter of claims 20-23, 84 and 85, does not involve an inventive step (Art.33(3) PCT and R.65(1)(2) PCT), for the following reasons:

3.1. Document D1, just as much as document D2, can be considered to represent the most relevant state of the art. Its teaching is as described above.

3.2. The difference in terms of technical features between D1 and the subject-matter of claims 20-23, 84 and 85 lies in the definition of process steps of said claims. The process steps are not as accurately described in any of D1 or D2 but, no technical effect could be attributed to said process steps in particular, since the storage stability of the application's compositions and those of D1 or D2 do not markedly differ. Besides, processes comprising steps very similar to those of claims 20-23, 84 and 85 are described in e.g. D3 and D4.

3.3. Absent a corresponding technical effect, it must be concluded that the subject-matter of claims 20-23, 84 and 85 does not involve inventive activity in the sense of Article 33(3) PCT.

4. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

4.1. The subject-matter of all claims would find industrial applicability e.g. in the preparation of storage stable vaccine compositions.

Reasoned statement with regard to novelty, inventive step or industrial applicability of invention 3:

2. NOVELTY (Art. 33(2) PCT)

2.1. Claims 24-42 and 86-104 appear to be novel, since no document of the available prior art appears to disclose a method comprising the freezing of at least 50 ml of liquid virus composition for at least about 20 minutes in a liquid nitrogen bath followed by lyophilisation. Also claims 58 and 61 appear to be novel, in so far as they relate to RSV, since the available prior art does not describe an RSV composition obtainable by the process of claims 24-42 (i.e. less than 1log10 loss of titer). If the " less than 1log10 loss of titer" could be ascertained for the subject-matter of claims 58 and 61 in so far as they relate to PIV, and for claims 120 and 123, they could be also be considered to meet the novelty requirement. Such is however not the case at present, since the application provides data only for RSV, and no principle fit for generalisation could be found, such that claims 58 and 61 in so far as they relate to PIV, and claims 120 and 123 are not distinguishable from, and therefore not novel over, any frozen batch of said viruses.

3. INVENTIVE STEP (Art. 33(3) PCT)

3.1. D6 can be considered to represent the closest prior art. It notably indicates (Table on p.24) that pre-freezing temperatures of virus compositions are -50C or colder. Shell freezing is notably mentionned as an option. The difference between D6 and the subject-matter of claim 24 is pre-freezing in a liquid nitrogen bath. In the light of application's example 4, the tecnical effect of said difference is obtention of freeze-dried composition characterised by comparatively low loss of potency. Pre-freezing in a liquid nitrogen bath has been amply described in the context of freeze-drying of small samples (e.g. D7). However, no document has been found to suggest its application to the pre-freezing of liquid virus compositions having a volume of at least 50 ml, nor the corresponding improvement in loss of potency. Now, since the rate of pre-freezing is known in the prior art to directly influence the outcome of freeze-drying, and since the technical effect has been demonstrated for RSV compositions (example 4), claims 24-42, 58 and 61, in so far as they relate to the processing of RSV, can be considered to meet the requirement of Article

33(3) PCT. However, no basis for generalisation could be found in the application, and no technical effect has been demonstrated for PIV, nor for any other virus mentionned in claims 86-104, 120 and 123. Claims 24-42, 58 and 61, in so far as the relate to the processing of PIV, and claims 86-104, 120 and 123 cannot be considered to meet the requirement of Article 33(3) PCT since, absent a corresponding technical effect, the use of liquid nitrogen for pre-freezing must be considered part of what the skilled person would have contemplated without exercising inventive activity in the light of D6 and D7.

4. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

4.1. The subject-matter of all claims would find industrial applicability e.g. in the preparation of bulk storage stable vaccine compositions.

Reasoned statement with regard to novelty, inventive step or industrial applicability of invention 4:

2. NOVELTY (Art. 33(2) PCT)

2.1. Claims 121 and 124 lack novelty (Art. 33(2) PCT) in the light of D8, which describes (p.1906 col.2 par.1) live attenuated influenza virus composition in a nasal-spray device stored frozen at -70C (the so-called "Flumist"). It is noted in this respect that the application provides data, in respect of invention 4, only for RSV compositions, and that no concept fit for generalisation is apparent, such that the compositions of claims 121 and 124 are not distinguishable from the vacine formulations frozen in a nasal spray device of D8.

3. INVENTIVE STEP (Art. 33(3) PCT)

3.1. The subject-matter of claims 43-56, 59 and 62, in so far as these relate to PIV, and of claims 105-118 do not meet the requirement of Art. 33(3) PCT, for the following reasons: The application provides data, in respect of invention 4, only for RSV compositions (example 5) and no concept fit for generalisation is apparent. A technical effect of the claimed freezing method can only be acknowledged for RSV compositions (storage stability in Table 9 vs Table 10, Table 11 vs Table 12). Hence, absent a corresponding technical effect, the subject-matter that does not relate to RSV compositions cannot be considered inventive over e.g. D8, since freezing by heat transfer is one of several, equally suitable alternatives available in the prior art to the skilled person.

3.2. A technical effect has been demonstrated for the method as claimed applied to RSV

compositions (example 5). For that subject-matter, D9 can be considered to represent the closest prior art. It teaches RSV vaccine formulations for intranasal administration. The subject-matter of present claims 43-56, 59 and 62, in so far as these relate to RSV compositions, can be considered to meet the requirement of Art 33(3) PCT, since nowhere in the prior art was indicated that the claimed freezing method would result in such low rates of potency loss (Table 9 vs Table 10, Table 11 vs Table 12).

4. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

4.1. The subject-matter of all claims would find industrial applicability e.g. in the preparation of storage stable vaccine compositions in nasal spray devices.